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(71) 出願人 スミスクライン・ビーチャム・パブリック・リミテッド・カンパニー
イギリス国ミドルセックス・ティードブリュ8・9イービー、ブレンフォード、ニュー・ホライズンズ・コート (番地の表示なし)
(72) 発明者 ギャザード, ブライアン・ジョージ
イギリス国ロンドン・エスダブリュ1、ホースフェリー・ロード、ディーン・ライル・ストリート、ザ・ウエストミンスター・ホスピタル (番地の表示なし)
(74) 代理人 弁理士 青山 蓑 (外1名)

(54) 【発明の名称】 ミクロスポリディア症の治療におけるベンゾイミダゾール駆虫薬の使用

(57) 【要約】

ミクロスポリディア症の治療におけるベンゾイミダゾール駆虫薬の使用。

1. ミクロスポリディア症の治療用薬物の製造用ベンゾイミダゾール駆虫薬。
2. ベンゾイミダゾール駆虫薬がアルベンダゾールである請求項1記載の使用。
3. 感染される患者がヒト免疫不全ウイルス（HIV）にも感染している請求項2記載の使用。
4. ミクロスポリディア症が下痢の原因となる感染である請求項3記載の使用。

ミクロスポリディア症の治療におけるベンゾイミダゾール駆虫薬の使用

本発明は、ミクロスポリディアによって引き起こされる疾患の治療、特に、ヒト免疫不全ウイルス（HIV）に感染している患者の下痢の治療における、ある種のベンゾイミダゾール化合物の使用に関する。

腸物が感染するプロトゾア・ミクロスポリディア（*protona microsporidia*）は500種類を超える。急性免疫不全症候群（AIDS）の出現までは、ヒト感染は珍しく、1、2件の腸炎および肺炎に限られていた。しかしながら、現在、ミクロスポリディア症は、HIV感染患者の集団において共通しており、下痢の原因と考えられる。アメリカ合衆国における最近の研究では、下痢の原因として他の病原体が排除されていない患者の3分の1は、空腸生検中にミクロスポリディア菌感染を持つことが判明した【ヒューマン・パソロジー（*Human Pathology*）, 1990, 21（5）, 475-82】。最近、英国の研究では、非常に類似の形態が得られた【ピーコック（*Peacock*）ら、ジャーナル・オブ・クリニカル・パソロジー（*J. Clin. Path.*）1991, 印刷中】。しかしながら、ミクロスポリディア菌が下痢の原因において病原体的重要性を有するものであるという重要な証拠は、好適な化学的治療剤でこの微生物を全滅させる能力、または、別法として、好適な動物モデルの開発を必要とする。かかる好適な化学的治療剤は、現在でも、入手可能ではない。

本発明は、この要求を満たすものであり、第1の態様において、ヒト免疫不全ウイルス（HIV）に感染している患者における、ミクロスポリディア症の治療、特に、例えば、下痢の原因となるミクロスポリディア症のようなミクロスポリディア症の治療用薬物の製造において使用するためのベンゾイミダゾール駆虫薬アルベンダゾールを提供するものである。

より広範囲の態様において、本発明は、ヒト免疫不全ウイルス（HIV）に感

染している患者における、ミクロスポリディア症の治療、特に、下痢の原因となるミクロスポリディア症のようなミクロスポリディア症の治療用薬物の製造において使用するためのベンゾイミダゾール駆虫薬を提供するものである。

「ベンゾイミダゾール駆虫薬」なる語は、広義駆虫薬として作用することが知られているいずれのベンゾイミダゾール含有薬物をも含むことを意図する。例えば、かかる化合物としては、アルベンダゾールに加えて、フェンベンダゾール、オキシベンダゾール、メベンダゾールおよびバルベンダゾールが挙げられる。

さらなる態様では、本発明は、ミクロスポリディア症の治療が必要な対象に、例えばアルベンダゾールのようなベンゾイミダゾール駆虫薬の有効量を投与することからなる、ミクロスポリディア症の治療方法を提供する。特に、本発明は、ヒト免疫不全ウイルス（HIV）に感染している患者において、ミクロスポリディア症、例えば、下痢の原因となるミクロスポリディア症の治療方法を提供する。

本発明で使用する場合、活性剤は、標準的な医薬組成物、例えば錠剤組成物に賦形化される。

活性剤の好適な用量は、1日当たり100～5000mgの範囲であり、該化合物は、症状を加重し、かつ、患者の感染からの解放を維持することが必要である限りは、1個以上の離散性投与単位で、1日1回または2回、投与される。用量計量性のサイズ、回数および期間は、もちろん、感染の重症度に左右されるであろう。

結果

下痢を有し、空腸生検でミクロスポリディア症を示した6体のHIV感染患者で研究を行った。

該患者をアルベンダゾール（400mg, b. i. d.）で、1週間以内で投与し、6体のうち5体は、下痢が完全になくなるという劇的な症候性改善があり、体重低下が阻止された。結果として、2体の患者は、非下痢性の原因で死亡し、1カ月の治療を完了した残りの4体のうち2体は再感染した。

これらの患者のうちの5体において治療の後に空腸生検によって、ミク

ロスポリディア菌の感染の継続が示されるが、明らかな成熟は阻止され、その結果、顕著なモロト期が見られるが、成熟幼虫はない。

圖書室

PGI/DR 92/00522

[illegible]

International Application No. PCT/GB 92/00122

| IS PROCEZNOI CONSIDERED TO BE SELF-DEFENDING | | CONTINUED FROM THE PREVIOUS SHEET | |
|--|---|-----------------------------------|--|
| Category | Details of Discovery and Description, with explanation of the relevant passage | Category | Details of Discovery and Description, with explanation of the relevant passage |
| P.2 | J. Protezno, volume 38, no. 6, 1971, Society of Proteznoists, 1991; E.U. Canney et al.: "In vitro and in vivo investigations of human microsporidia", pages 631-635, see page 634 | 3.2 | |

國際調查報告

CN 9200522
 SA 57702

The above data are purely tentative evidence relating to the patent documents cited in the above-mentioned interdictory search report. The numbers are as contained in the European Patent Office EDP file on 97/07702. The European Patent Office is in no way liable for these provisions which are merely given for the purpose of information.

| Patent document date to search report | Publication date | Patent family number(s) | Publication date |
|--|---------------------|----------------------------|---------------------|
| FR-9- | 4763 | None | |

For more details about this course, see *Official Journal of the European Patent Office*, No. 12/92

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁵ : A61K 31/415 | A1 | (11) International Publication Number: WO 92/16208 (43) International Publication Date: 1 October 1992 (01.10.92) |
| (21) International Application Number: PCT/GB92/00522 (22) International Filing Date: 23 March 1992 (23.03.92) (30) Priority data: 9106278.6 25 March 1991 (25.03.91) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : GAZZARD, Brian, George [GB/GB]; The Westminster Hospital, Dean Ryle Street, Horseferry Road, London SW1 (GB). | (74) Agents: GIDDINGS, Peter et al.; Corporate Patents, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i> | |
| (54) Title: USE OF BENZIMIDAZOLE ANTHELMINTIC IN THE TREATMENT OF MICROSPORIDIAL INFECTIONS (57) Abstract The use of a benzimidazole anthelmintic in the treatment of microsporidial infection. | | |

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USE OF A BENZIMIDAZOLE ANTHELMINTIC IN THE TREATMENT OF MICROSPORIDIAL INFECTIONS

The present invention relates to the use of certain benzimidazole compounds in the treatment of diseases caused by microsporidia organisms, in particular the treatment of diarrhoea in patients infected with human immunodeficiency virus (HIV).

There are more than 500 species of the protozoa microsporidia which infect animals. Until the advent of acquired immune deficiency syndrome (AIDS) human infection was rare and confined to one or two cases of encephalitis and myositis. Now, however, microsporidium infection is common in the small intestine of HIV infected individuals and is thought to cause diarrhoea. In a recent study in the USA a third of patients in whom no other pathogen as a cause of diarrhoea had been uncovered, were found to have microsporidiosis infection in jejunal biopsy material (Human Pathology, 1990, 21(5), 475-81). Very similar figures were recently obtained in a UK study (Peacock et al., J. Clin. Path. 1991, in press). However, positive proof that Microsporidiosis is of pathogenic importance in the development of diarrhoea requires the ability to eradicate this organism with suitable chemotherapeutic agents or, alternatively, the development of suitable animal models. Such suitable chemotherapeutic agents have, until now, not been available.

The present invention fulfils this need and provides in a first aspect, the benzimidazole anthelmintic albendazole, for use in the manufacture of a medicament for use in the treatment of microsporidia infections, in particular in the treatment of microsporidia infection, for example diarrhoea-causing microsporidial infection, in patients infected with the human immunodeficiency virus (HIV).

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In a broader aspect, the invention provides a benzimidazole anthelmintic for use in the manufacture of a medicament for use in the treatment of microsporidia infections, in particular in the treatment of microsporidia infection, for example diarrhoea-causing microsporidia infection, in patients infected with the human immunodeficiency virus (HIV).

The term 'benzimidazole anthelmintic' is intended to include any benzimidazole containing agent which is known to act as a broad spectrum anthelmintic. For example, in addition to albendazole, such compounds include fenbendazole, oxibendazole, mebendazole and parbendazole.

In a further aspect the present invention provides a method of treatment of microsporidial infection which comprises administration to a subject in need thereof of an effective amount of a benzimidazole anthelmintic, for example albendazole. In particular the invention provides a method for the treatment of microsporidial infection, for example diarrhoea-causing microsporidial infection, in patients infected with the human immunodeficiency virus (HIV).

When used in the present invention, the active agent is formulated in a standard pharmaceutical composition, for example in a tablet composition.

Suitable doses of active agent will be in the range of from 100 to 5000mg per day, the compound being administered in one or more discrete dosage units, once or twice a day, for as long as is necessary to treat the condition and maintain the patient free of infection. The size, frequency and duration of the dosage regimen will, of course, depend on the severity of the infection.

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RESULTS

A study was carried out on 6 HIV infected individuals with diarrhoea and proven microsporidial infection on
5 jejunal biopsy.

The patients were treated with albendazole (400mg, b.i.d.) and within 1 week, 5 of the 6 had had dramatic symptomatic improvement with complete loss of diarrhoea and
10 arrested weight loss. Subsequently, two patients died of non-diarrhoeal causes and of the remaining 4 who completed one month's treatment, two relapsed.

Jejunal biopsies performed following therapy in five of
15 these patients have shown continuing evidence of Microsporidiosis but an apparent maturation arrest so that frequent meronts are seen but mature spores are not.

CLAIMS:

1. A benzimidazole anthelmintic for use in the manufacture of a medicament for use in the treatment of microsporidial infection.
2. The use according to claim 1 in which the benzimidazole anthelmintic is albendazole.
3. The use according to claim 2 in which the patient treated is also infected with human immunodeficiency virus (HIV).
4. The use according to claim 3 in which the microsporidial infection is a diarrhoea-causing infection.

INTERNATIONAL SEARCH REPORT

International Application

PCT/GB 92/00522

| I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 31/415 | | | | | | | | | | | | | | |
|---|---|-------------------------------------|--|--|--|--|--|---|-----|--|-----|-----|---|-----|
| II. FIELDS SEARCHED <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; padding: 5px;">Classification System</td> <td style="padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="padding: 5px;">Int.C1.5</td> <td style="padding: 5px;">A 61 K</td> </tr> </table> <p style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched⁸</p> | | | Classification System | Classification Symbols | Int.C1.5 | A 61 K | | | | | | | | |
| Classification System | Classification Symbols | | | | | | | | | | | | | |
| Int.C1.5 | A 61 K | | | | | | | | | | | | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; padding: 5px;">Category¹⁰</th> <th style="width: 70%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">FR,M, 4761 (CHIMETRON) 20 February 1967, see page 1, left-hand column, lines 1-15 ---</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">P,X</td> <td style="padding: 5px;">AIDS Care, volume 3, no. 4, 19 December 1991, E.K. Bagdades: "Current treatment of opportunistic infections in HIV diseases", pages 461-466, see page 464 ---</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-4</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">P,X</td> <td style="padding: 5px;">STN Information Service, file BIOSIS, abstract number 91:446850, "Treatment of intestinal *microsporidiosis* with albendazole", VII International Conference on Aids: Science Challenging Aids; Florence, IT, June 16-21, 1991, 464P, (vol. 1); 460P, (vol. 2), see the whole article --- -/-</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-4</td> </tr> </table> | | | Category ¹⁰ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | X | FR,M, 4761 (CHIMETRON) 20 February 1967, see page 1, left-hand column, lines 1-15 --- | 1 | P,X | AIDS Care, volume 3, no. 4, 19 December 1991, E.K. Bagdades: "Current treatment of opportunistic infections in HIV diseases", pages 461-466, see page 464 --- | 1-4 | P,X | STN Information Service, file BIOSIS, abstract number 91:446850, "Treatment of intestinal *microsporidiosis* with albendazole", VII International Conference on Aids: Science Challenging Aids; Florence, IT, June 16-21, 1991, 464P, (vol. 1); 460P, (vol. 2), see the whole article --- -/- | 1-4 |
| Category ¹⁰ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | | | | | | | | | | | | |
| X | FR,M, 4761 (CHIMETRON) 20 February 1967, see page 1, left-hand column, lines 1-15 --- | 1 | | | | | | | | | | | | |
| P,X | AIDS Care, volume 3, no. 4, 19 December 1991, E.K. Bagdades: "Current treatment of opportunistic infections in HIV diseases", pages 461-466, see page 464 --- | 1-4 | | | | | | | | | | | | |
| P,X | STN Information Service, file BIOSIS, abstract number 91:446850, "Treatment of intestinal *microsporidiosis* with albendazole", VII International Conference on Aids: Science Challenging Aids; Florence, IT, June 16-21, 1991, 464P, (vol. 1); 460P, (vol. 2), see the whole article --- -/- | 1-4 | | | | | | | | | | | | |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div> | | | | | | | | | | | | | | |
| IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center;">01-06-1992</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center;">4 JUL 1992</div> </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="text-align: center;">Mme N. KUIPER </div> </td> </tr> </table> | | | Date of the Actual Completion of the International Search <div style="text-align: center;">01-06-1992</div> | Date of Mailing of this International Search Report <div style="text-align: center;">4 JUL 1992</div> | International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> | Signature of Authorized Officer <div style="text-align: center;">Mme N. KUIPER </div> | | | | | | | | |
| Date of the Actual Completion of the International Search <div style="text-align: center;">01-06-1992</div> | Date of Mailing of this International Search Report <div style="text-align: center;">4 JUL 1992</div> | | | | | | | | | | | | | |
| International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> | Signature of Authorized Officer <div style="text-align: center;">Mme N. KUIPER </div> | | | | | | | | | | | | | |

| III. DOCUMENTS CONSIDERED TO BE RELEVANT | | Relevant to Claim No. |
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| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | |

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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
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| FR-M- 4761 | | None | |

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